The Frequency Dependence of Osmo-Adaptation in *Saccharomyces cerevisiae*

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Introduction

Goal: Gain biological insight into cellular activity using a signal processing perspective.

Approach:

- Measure the frequency response of the cell for a wide range of frequencies,
- Model the cell as a LTI system.
- Confirm model by predicting the response of the cell for different inputs.
- Interpret the model biologically to infer the dominate processes.

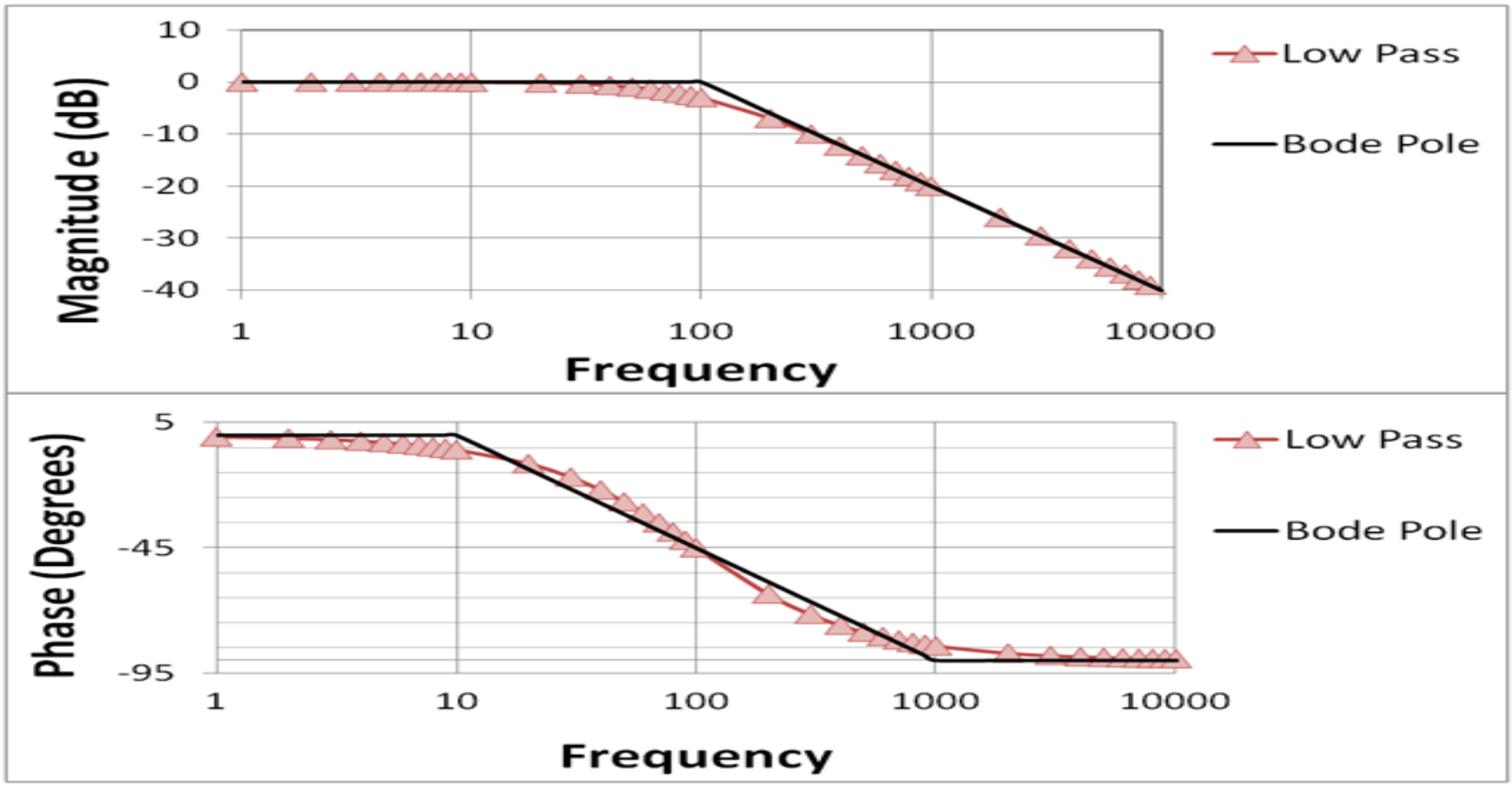
6.003 Background

A linear, time invariant system can be fully characterized by its transfer function or frequency response function, which shows how the system modifies amplitude and phase for pure sine wave inputs at different frequencies.

You can get the frequency response function by just putting in different inputs and measuring the results.
(Remember Pset 5?)

Frequency Response

Bode plot is Frequency Response
-- this is a low pass filter.



Impulse Response

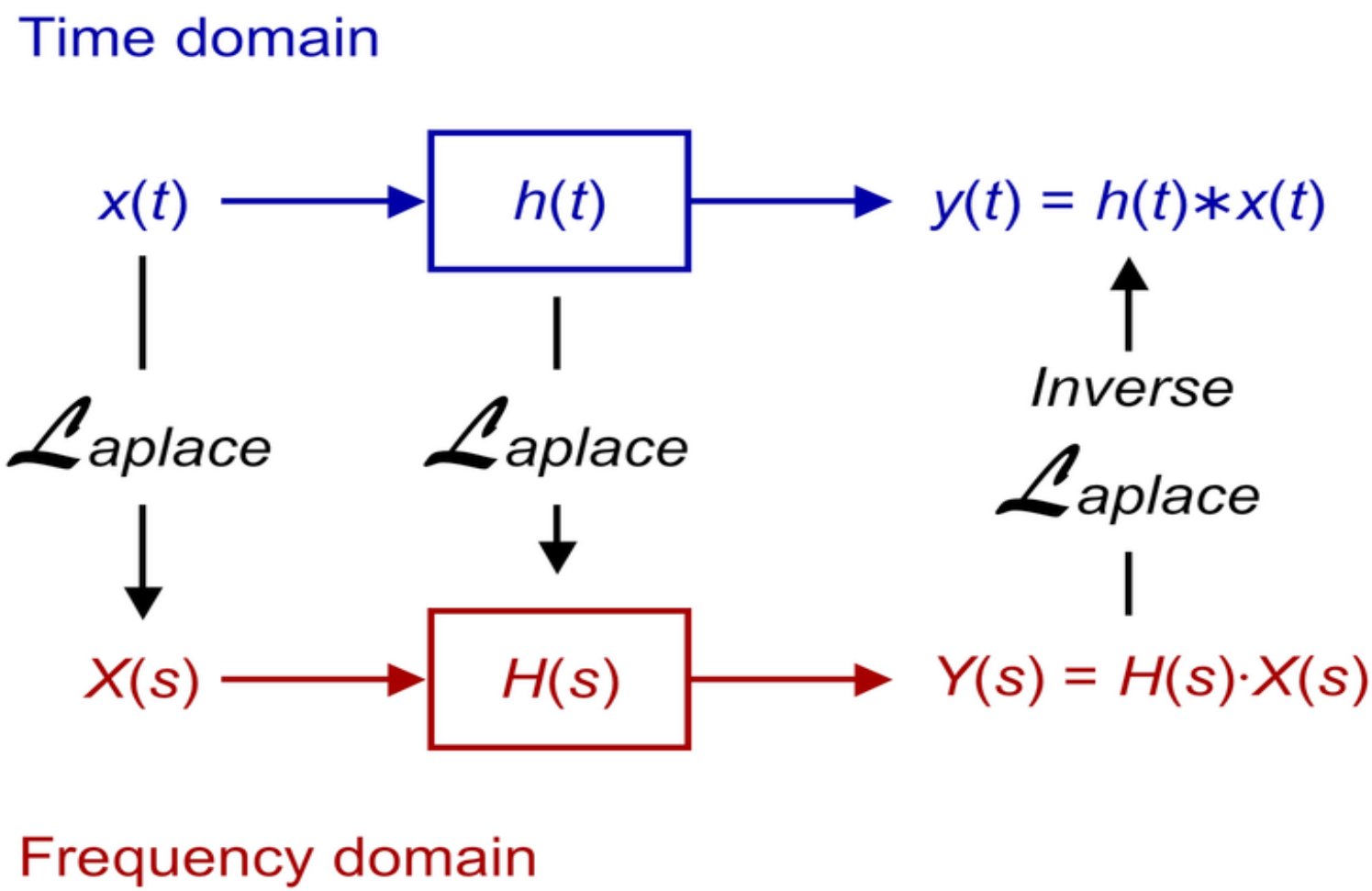
What does the system do when you hit it with a sudden spike?

That's the impulse response!

How do you find it?
Impulse has all frequencies equally, so take inverse Fourier transform of transfer function, and you get the Impulse response.

How do you get the response for other stuff? You *convolve* the im response with the stuff you actually want. That's why the impulse response is useful.

LTI System


Time domain
x(t)
h(t)
y(t) = h(t)∗x(t)
Laplace
Laplace
Inverse
Laplace
X(s)
H(s)
Y(s) = H(s)·X(s)
Frequency domain

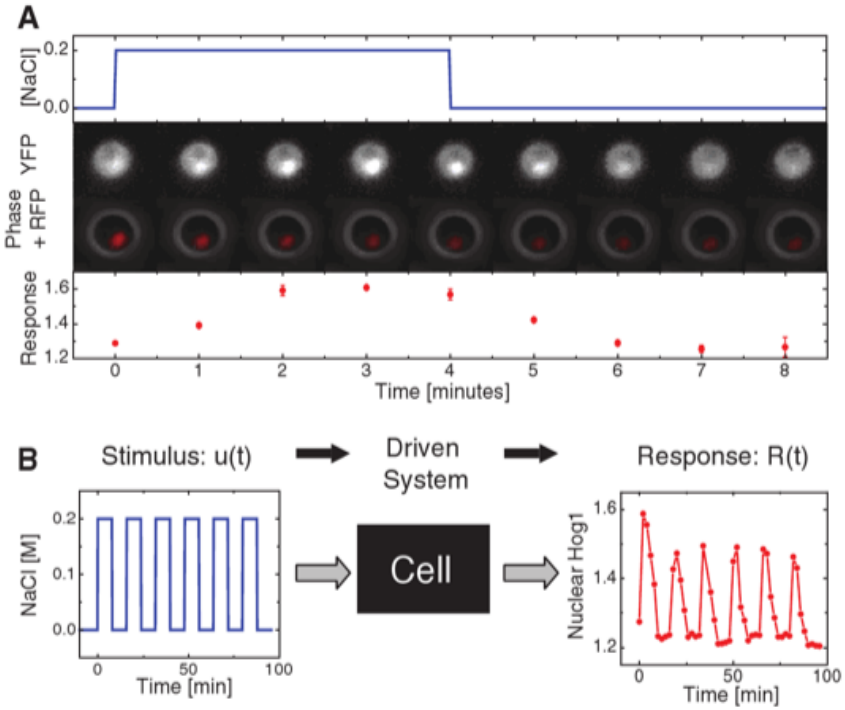
Biology background

High-osmolarity glycerol (Hog1) mitogen-activated protein kinase (MAPK) cascade in yeast *Saccharomyces Cerevisiae*

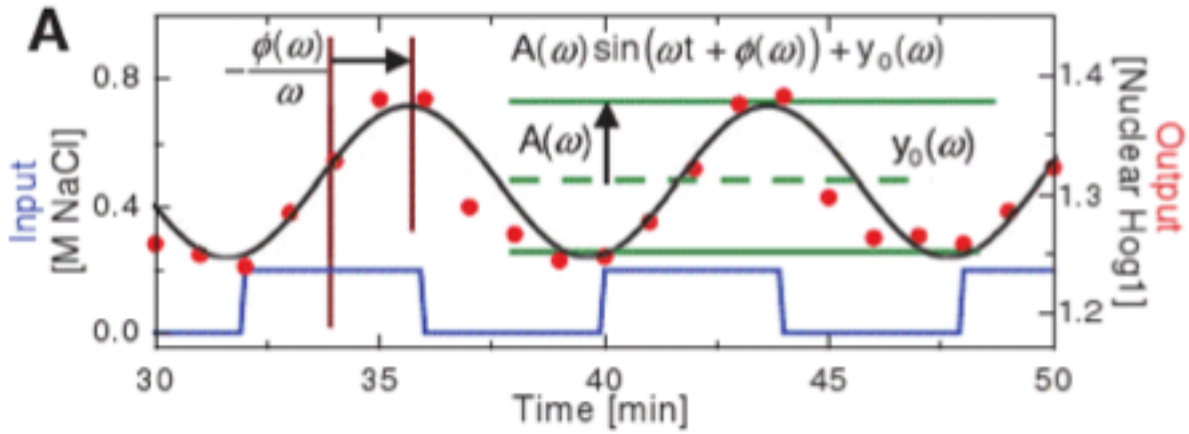
- input (extracellular osmolyte concentration) and output (activity of MAPK Hog1) are easily measured
- well studied network
- unclear which of the multiple negative feedback loops dominate

Methods

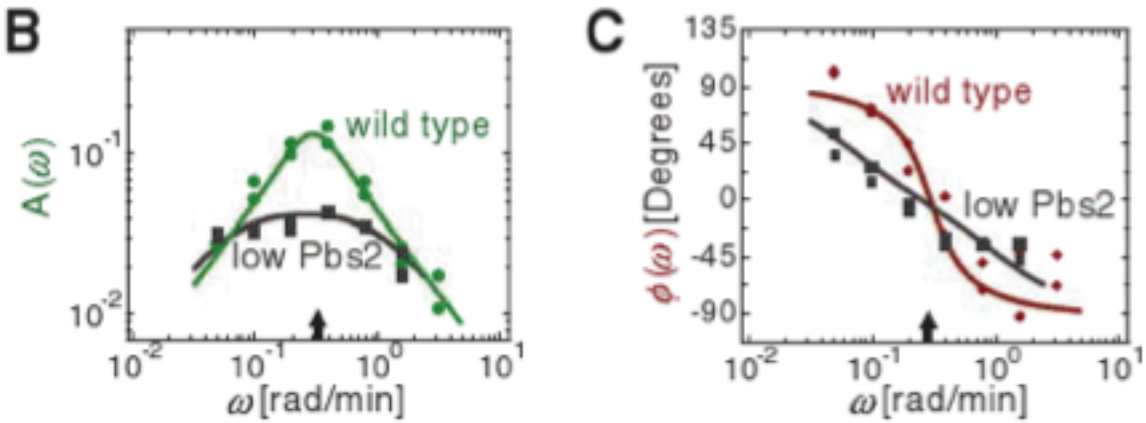
- In osmotic balance, Hog1 is primarily in the cytoplasm, reported by Hog1-YFP
- After hyperosmotic shock, Hog1 accumulates in the nucleus
- When osmotic balance is restored, Hog1 is exported from the nucleus
- $R(t) = ([YFP_{nucleus}]/ [YFP_{cytoplasm}])$ population



Results

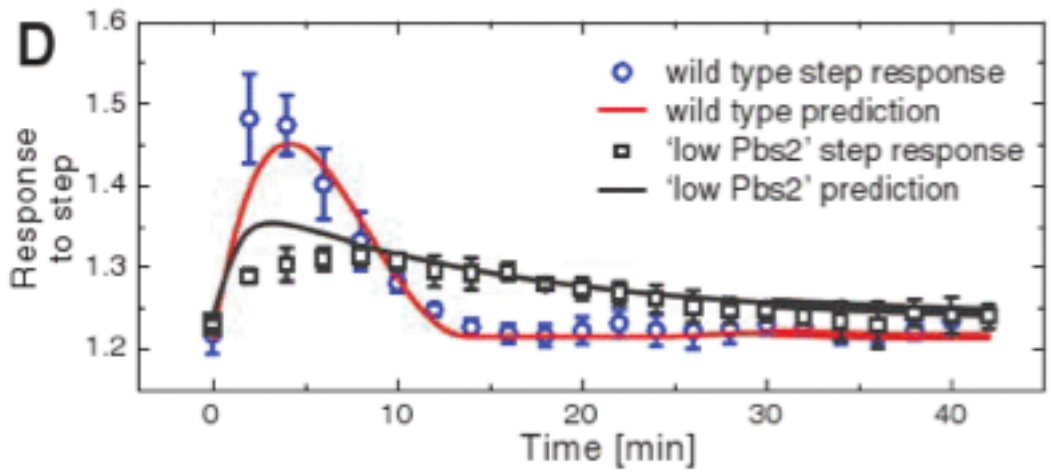


- Blue line: NaCl concentration
- Red circle: net Hog1-YFP response



Results

- Derived impulse response
- Made prediction of step input of 0.2 M NaCl

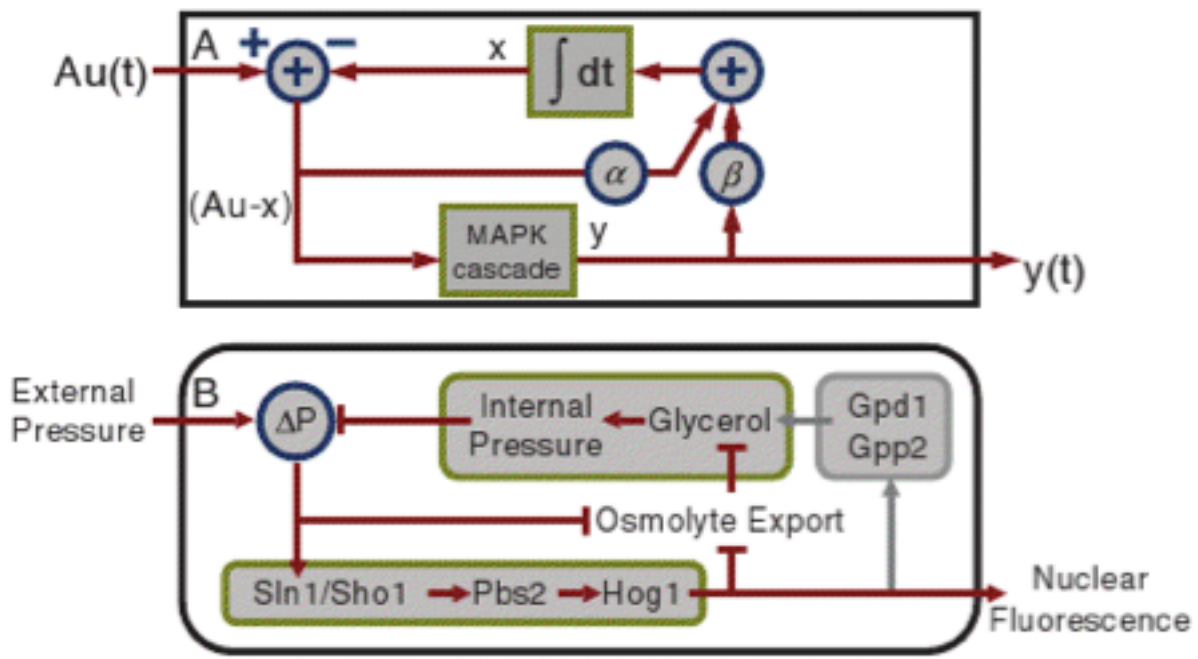


Results

- Rewrote LTI model in terms of two feedback loops
- Compared against biological model

$$\dot{y} = (A_0 u - x) - \gamma y$$

$$\dot{x} = \alpha(A_0 u - x) + \beta y$$



Analysis

- From the feedback model, one pathway is Hog1-dependent and another is Hog1-independent
- Both pathways operate at different timescales
- This is confirmed by known biological models of yeast intracellular osmolyte regulation

Conclusion

- Current model of MAPK's role is osmoregulation is incomplete
- Model suggests gene expression plays minimal role in hyperosmotic shock
- Results show nontranscriptional feedback occurs on short timescales and gene transcription happens for intense shocks on long timescales
- **Applying engineering principles could help determine effective network structures**